

EDITORIAL

A Voice for Medicine in the West

THE WESTERN JOURNAL OF MEDICINE is being published by the California Medical Association as a voice for medicine in the West. It has been more than five years since the Council of the association directed the editors of CALIFORNIA MEDICINE to point toward the publication of a truly regional medical journal. The need for such a journal is obvious enough, and it has now come into being.

THE WESTERN JOURNAL OF MEDICINE is not really a new journal. Rather it is a natural outgrowth of a distinguished predecessor, CALIFORNIA MEDICINE, which felt that there was a larger job to be done. The three western coastal states have ten schools of medicine, and their medical associations have proven records of innovation and successful accomplishment. The vitality and achievements in science, education and practice which are the hallmarks of medicine in the western United States now need a stronger presence in the medical literature which records and shares advances and progress with the medical community in the nation and indeed the world. THE WESTERN JOURNAL OF MEDICINE hopes to give medicine in the West this presence and this recognition.

The opportunity is great and there is much to be done. The editors cannot do it alone. We are proud of the new Editorial Board. But we need and solicit the help of the medical community, the medical associations, the medical schools, the allied health professions, and especially physicians and physicians-to-be in research, academia, practice, and in the economics and politics of medical care. With the kind of help that should be available in this virile and vital region of the United States, THE WESTERN JOURNAL OF MEDICINE should indeed become a voice for medicine in the West. Let us do what needs to be done—together.

The Ubiquitous Adenovirus

IN THE MORE THAN 20 years since it was first isolated, the adenovirus has established a number of virologic firsts: the first agent to be isolated from tissue explants;¹ the first of the "new" viral agents to be harnessed into an effective virus vaccine;² the first viral agents isolated from humans capable of producing a tumor in animals;³ and the first viral agent responsible for urinary tract disease.⁴ A special conference entitled "Potpourri of Adenoviral Infection" published elsewhere in this journal therefore seems appropriate and worthy of additional comment.

It was in 1953 that adenovirus was isolated from tissue explants and from patients with respiratory illness.¹ Thus adenovirus isolation was an early, important clinical result from the momentous discovery of Enders, Weller and Robbins that viruses may easily be propagated in culture cell lines—a discovery which led to numerous scientific contributions and opened the door to the golden age of virology.

The adenovirus was soon found to be the etiologic agent for a variety of clinical syndromes. An important contribution in those early years was the discovery that acute respiratory disease (ARD), a common illness among military recruits, was caused by adenoviruses.⁵ While this important etiologic and epidemiologic work was going on, concurrent work in the laboratory identified their biologic, physicochemical and immunologic properties. It was this information which made it possible to characterize human adenoviruses into 31 distinct immunological types. It was soon discovered, however, there was a common immunologic protein in all of these adenoviruses which made possible species identification on the basis of a simple complement fixation test.

Much of the early enthusiasm and intensive work on adenoviruses was based on the assump-

tion that these agents were responsible for a large percentage of respiratory disease in the general population just as in the case of military recruits. Therefore, isolation and characterization of these agents were followed in short order by the production of an effective adenoviral vaccine.² With further investigation, however, it became apparent that adenoviruses were not responsible for the bulk of respiratory illness in the civilian population. Data from a variety of sources established the fact that adenoviruses were probably responsible for no more than 5 percent of respiratory illness in the non-military population.⁶ In essence, this left us with a vaccine in search of a disease—a true mark of an affluent society. The appreciation of differences in disease dynamics in different population groups was an important lesson which was not forgotten in subsequent infectious disease investigations.

Despite the fact the adenoviruses play only a small role in acute respiratory diseases in the civilian population, they are responsible for a wide variety of diseases involving many organ systems. These agents are frequently associated with tonsillopharyngitis or follicular conjunctivitis, which are mild infections. On occasion, however, adenoviruses may cause serious disease. Two of the cases discussed by Connor and his associates in the adenoviral conference emphasize this point. One case was that of a nine-month-old boy who had severe membranous conjunctivitis caused by adenovirus type 7. The second case was that of a ten-month-old infant with severe bilateral bronchopneumonia complicated by encephalitis. In this case, adenovirus type 7 was isolated from a tracheal specimen. Since both of these diseases can be caused by a variety of bacterial agents as well as by other viral agents, it is important to establish a diagnosis as early as possible so that appropriate therapy can be instituted, specifically with antibiotics in instances of bacterial infections. On the other hand, the complications and futility of antibiotic therapy can be avoided if one can with assurance establish a viral cause for a specific clinical entity.

The cases also serve to highlight some of the problems that still confront us with the diagnosis and treatment of adenoviral infection. Great strides have been made recently in facilitating rapid identification of a variety of viral agents. For example, the use of fluorescent antibodies makes it possible to establish, in a matter of hours, a diagnosis of herpes simplex and zoster infection,

rabies or smallpox. However, there is still a need to develop inexpensive, rapid, simple and reliable diagnostic procedures that can be performed in most hospital laboratories for many viral agents, including adenoviruses. In addition, there is a need for specific therapy against viral agents, including adenoviruses, which are responsible for life-threatening illnesses. This assumes greater importance when one realizes that in addition to causing acute debilitating disease, with its concurrent morbidity and mortality, permanent sequelae may result from adenoviral infections, particularly in children under two years of age. For example, there are three recent reports involving almost a hundred infants and children infected with adenovirus type 7 or 21.⁷⁻⁹ Disease resulted in death in about 6 percent of the patients. Lung fibrosis or segmental obstructive disease was noted in 25 percent of survivors while 16 percent had residual bronchiectasis. While these cases occurred during epidemics, sporadic adenoviral illness may also cause serious disease. We have recently seen an 18-month-old child with such an acute illness caused by adenovirus type 7 infection. This child was in hospital for 27 days and was near death during the height of her illness. Even ten months after discharge from the hospital this child was still dyspneic and had evidence of bronchiectasis and unresolved pulmonary infiltrates.

The association of certain types of adenoviral infections with serious illness in infants leads perhaps to a reconsideration of the usefulness of adenoviral vaccine as a preventive measure against these diseases. The introduction of the first adenovirus vaccine was premature. Work with a variety of other viral vaccines over the past ten to fifteen years has demonstrated the extreme caution that must be exercised in vaccine development. Should a virus selected for a vaccine be attenuated or inactivated? What is the best route of administration? What are the untoward effects, short term and long term? Can we arrive at a risk:benefit ratio from the use of this vaccine?

It is clear that these and other questions must be answered for every viral vaccine individually. Principles that have been learned from one viral vaccine may not be applicable to another. For example, inactive poliomyelitis virus vaccine is effective and safe. Inactive measles vaccine and respiratory syncytial virus vaccine stimulate antibody production but may be associated with an exaggerated clinical response when the vaccinee makes contact with the wild virus.

Experimental trials utilizing attenuated adenovirus vaccine types 4 and 7 are under way in the military.¹⁰ The vaccine, administered orally in an enteric coated capsule, produces protective antibody. Administering enteric coated material to infants below two years of age presents one of the immediate problems that must be considered. In any case, it is clear that a great deal of thought and work must take place before an adenoviral vaccine is introduced for general use.

Another clinical aspect of respiratory adenoviral infection type 1 and type 5 is worthy of note. Recent evidence suggests these viruses may be primary etiologic agents or co-conspirators in producing the whooping cough syndrome. Precise definition of adenoviruses in this syndrome awaits further epidemiologic and experimental data.¹¹

The small percentage of clinically apparent adenoviral respiratory disease may give the impression that we rarely encounter this agent. This is not true. The ubiquitousness of the adenoviruses is attested by the fact that 50 to 70 percent of infants inherit transplacental adenoviral antibodies.⁶ This demonstrates that a large percentage of people have been exposed before the child-bearing age. If respiratory disease does not account for this exposure, we must look to subclinical infection or other clinical manifestations of adenoviruses as the antigenic stimulus for antibodies found in a great portion of the population. Subclinical infections undoubtedly occur and the manifestation of adenoviral infection in organ systems other than respiratory or ophthalmologic has been amply documented.

Another and more recently recognized facet of adenoviral disease involves infection of the mesenteric lymph nodes. Mesenteric lymphadenitis may be difficult to differentiate from acute appendicitis. More important, enlarged mesenteric nodes or enlarged Peyer's patches of the ileum may be due to adenovirus infection. Recent studies have suggested this mesenteric node inflammation and enlargement or ileocecal valve inflammation may result in intussusception in a number of cases which have previously been designated as "idiopathic."¹²

A fascinating aspect of mesenteric lymph gland involvement was described in one of the cases presented in the current adenoviral conference reported elsewhere in these pages.⁵ The character of the lymph nodes on exploratory laparotomy of a four-year-old child suggested a lymphoproliferative

disease rather than a primary inflammatory illness. Cultures from a variety of orifices and the lymph node yielded organisms ultimately identified as adenovirus type 1. The potential of adenovirus for stimulating tissue proliferation recalls the observations of Huebner.³ In 1962 he produced sarcomas by inoculating adenoviruses into the cheek-pouches of hamsters. Production of these tumors involved adenoviral types not usually associated with human disease. Two years later Girardi induced sarcomas by use of adenovirus type 7, a common human pathogen.¹³ A number of investigations that followed were unable to incriminate adenovirus in human oncologic disease. Most of the studies involved an unsuccessful attempt to isolate the viral agent from tumor extracts. These results are not unexpected, since adenoviral tumors produced in experimental animals do not yield infectious virus. However, as investigations with more sophisticated techniques are undertaken it may be found that the last chapter of adenoviral involvement in human tumors has not yet been written.

The ubiquitous adenovirus has also been incriminated in urinary tract disease. Hemorrhagic cystitis has been associated with adenovirus type 11.⁴ Indeed, it is the only viral agent to date definitely associated with disease in this organ system.

The investigations over the past 20 years have incriminated adenovirus as an etiologic agent of a number of diseases. They have also provided provocative inquiries into oncogenic properties of viral agents. Although many of the infections with which adenoviruses are associated are mild, on occasion they may be the etiologic agents of serious illness with significant morbidity and mortality. It is doubtful that we have heard the last of the disease-producing capabilities of the adenoviruses.

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Cigarette Smoking Ten Years Later

IT IS NOW JUST TEN YEARS since cigarette smoking was officially designated a health hazard by the federal government. What has been accomplished is worthy of some examination.

To start at the beginning, it has been more than four hundred years since tobacco was discovered in the Americas and the habit of smoking was transferred to France (1556), Portugal (1558), Spain (1559) and England (1565). It has been over a hundred years (1859) since 68 patients in a hospital in Montpelier, France, were found to have cancer of the lips, tongue, tonsils or elsewhere in the mouth. Sixty-six of these smoked short clay pipes and the use of such pipes soon thereafter fell into disrepute. In 1954 the American Cancer Society and the British Medical Research Council in separate studies observed a higher death rate among cigarette smokers than among non-smokers. In 1962 the Royal College of Surgeons found cigarette smoking a serious hazard to health. In 1963 a second American Cancer Society report showed that death rates had increased over the years as the number of cigarette smokers increased. Just ten years ago, in January 1964, a Special Advisory Committee on Smoking and Health to the Surgeon General of the United States concluded that "cigarette smoking is a health hazard of sufficient importance in the United States to warrant remedial action." Subsequently a number of legal actions

were taken and the slogan "Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health" has been very widely published.

What has been accomplished by an all-out legally backed educational campaign over a period of a decade may now be examined. According to the Federal Trade Commission the per capita consumption for adults 18 and over was 4,345 cigarettes a year in 1963, 4,186 in 1968, and 4,040 in 1971, with indications that it has remained at about this level since. It also appears that the total number of cigarettes produced has remained fairly constant at something over 500 billion a year. Thus the crude statistical results appear to have been something less than dramatic. To be sure, some people have stopped smoking cigarettes, others no doubt have cut down, but many must also have started. The emphasis on less nicotine and less tar is not to be overlooked, and may have important beneficial effects on the death rates, but it is too early yet to know this. No matter how one looks at it, the results of what has been a very major health campaign over a period of a decade have been disappointing.

There is surely food for thought in this. Much less was accomplished than might have been expected. No doubt others more knowledgeable and statistically sophisticated than the writer will comment. But it seems likely that there are both pharmacological and human factors which have yet to be taken into full account. Drug dependency with all its physiological and psychological ramifications can make it difficult indeed for one who is addicted to cigarettes to quit his habit, and it is worth noting that the campaign addressed itself to health and not to drug dependence. And health and even longevity may not be the high priority for many persons that so often they are assumed to be. Indeed, there is considerable evidence to the contrary. People will often risk health and even survival for some purpose, whether good or bad, or for some momentary thrill or satisfaction. Their reasons for doing this may be either rational or irrational. But this fact of human nature thwarts many noble efforts in public health and preventive medicine, and in medical care as well. These are factors which seem particularly to have come into focus as the results of the ten-year effort to curtail cigarette smoking are examined. Perhaps the campaign for the next decade should take them into more account.

—MSMW